REMARKS

After entry of the above amendment, **claims 41 to 65 and 67 to 69** are now pending in the instant case.

Claims 41, 44-46, 50, 52, 55, 56, 63, 65 and 67 have been amended in order to better define what the Applicant considers his invention, as fully supported by an enabling disclosure. **Claim 66** has been cancelled. Applicant reserves the right to prosecute the subject matter of cancelled or amended claims in further applications.

Further support for the amendments can be found in the application as originally filed. More particularly, support for "urine sample having not been obtained immediately following ejaculation", in **claim 41** (and **67**) can be found from the common and general definition of urine. Specific support is also found in paragraph **025** which relates to a general urine sample obtained without digital rectal examination (DRE), a urine sample obtained after DRE or "other types of samples such as sperm or mixed urine and sperm (e.g., first urine sample following ejaculation)". Support can also be found in paragraph **073** which relates to a urine sample following digital rectal examination, so as to increase the content of prostate cells in the sample. Paragraphs **132** and **138** provide further support for the general definition of urine sample following, or not, a digital rectal examination. Taken together, it should be understood, that the definition of urine as used in the claims prior to the present amendment related to regular urine samples (having not been obtained following ejaculation). This is clearly supported by the fact that sperm-containing samples are defined as "other types" of urine samples in the instant application. Nevertheless, for clarity, the claimed regular urine sample was further defined.

Further support for the amendments to **claim 41** related to a level of prostate cancer-specific PCA3 mRNA and its association with the risk of developing prostate cancer

or the presence or absence thereof, can be found in paragraphs **084** and **085** and more particularly in paragraphs **082** and **091**.

The amendments to claims **41, 44-46, 50,** and **67** to replace "second prostate-specific" by "prostate-specific" are but of an editorial form. Applicants believe that the combination of the detection of the "PCA3 prostate cancer-specific mRNA" and of a "prostate-specific mRNA" is clear and definite and that the deletion of "second" clarifies the claims. Support for the terminology "prostate-specific" can in any event be found for example in paragraph **069** "*As used herein the terminology ''prostate specific marker'' relates to any molecule whose presence in the sample indicates that such sample contains prostate cells (or a marker therefrom). Therefore a ''prostate specific sequence'' refers to a nucleic acid or protein sequence specifically found in prostate cells and usually not in other tissues which could ''contaminate'' a particular sample.*"

Further, **claim 45** has been amended to recite that the prostate-specific marker is a prostate-specific PCA3 mRNA that is not associated with prostate cancer, as clearly supported for example in paragraphs **084** and **105**.

The amendments to **claims 52 and 55** so as to specify that the beacons are not "any types" of beacons, but beacons which are specific to the sequence they target (e.g., PCA3 and PSA) can be found from the plain meaning of "beacon" in the application as filed, from the Sequence Listing, and from the disclosure such as in paragraphs **076, 115** (the latter defining beacons and explaining the principle of their mechanism of action [i.e., the beacon will not fluoresce when it is free in solution, and its conformation will change when the beacon specifically hybridizes to its target sequence thereby enabling the beacon to fluoresce]), **116** and **117** (relating to detection of PCA3 and PSA and teaching how to design molecular beacons).

The amendment to **claim 63,** which is mostly of an editorial nature, is supported by paragraph **073**.

Support for the amendments to **claim 67** can be found in the same location as that cited for claim 41 above, since the amendments to claim 67 are identical to those of claim 41.

Reconsideration in view of the following remarks and entry of the foregoing amendments are respectfully requested.

OBJECTIONS

The typographical error in **claim 56** has been corrected by the current amendment as suggested by the Examiner.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 41-69 have been rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as its invention. Applicants respectfully traverse this rejection.

Claims 41 and dependent claims 42-66 have been rejected firstly because the Examiner considers that the conclusionary statements of claim 41 "(d)" do not fully relate to the preamble of the claim. The Examiner believes that it is unclear how a measured level is being compared to a PCA3 mRNA sequence. The Examiner also objects to the "active step of 'correlating' " and the alleged lack of recitation as to how this correlation is indicative of a particular risk of developing prostate cancer or the presence thereof.

The Examiner secondly rejects **claims 41 and dependent claims 42-66** for similar reasons, but with reference to paragraph "(e)". Thus, the Examiner is of the view that

claims 41 and the dependent claims thereon, whether relating to a correlation of a level of PCA3 to a higher risk of developing prostate cancer or presence thereof or to a lower risk or absence of prostate cancer is indefinite and that the metes and bounds of the claims cannot be determined. The Applicant respectfully traverse the rejections as follows.

It is respectfully submitted that the amendments to claim 41 which delete the term "correlating" and which more specifically recite what is detected and how detection is indicative of the prostatic state of the patient, overcome the rejection. It should be clear from the teachings of the present invention that the detection of an elevated level of prostate cancer-specific PCA3 mRNA sequences and its comparison with the level thereof (or to a predetermined cut-off value) in a normal prostate, enables the determination as to whether the patient has or is predisposed to developing prostate cancer. It should also be clear from the disclosure that the absence or lower level of detection of prostate cancer-specific PCA3 mRNA sequences, as compared to that of a normal prostate (or to a predetermined cut-off value) is indicative of an absence or lower risk of developing cancer in that patient.

Taken together, the Applicant respectfully submits that claim 41 (and dependent claims 42-66) clearly define the metes and bounds of the claims.

The rejection of **claim 63** is submitted to have been overcome by the cancellation of the objected recitation concerning an increased number of prostate cells.

The rejection of **claim 67 and dependent claims 68-69** with reference to paragraph "(d)" and "(e)" (pages 5 and 6 of the Office Action) is submitted to have been rendered moot by the amendments to claim 67, as discussed above for the similar rejections concerning **claim 41 and dependent claims 42-66**.

In view of the above and foregoing, Applicant respectfully submits that claims 41 to 69 are definite and requests that the Examiner withdraws his rejection under 35 U.S.C. § 112, second paragraph.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION REJECTION)

Claims 41-69 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

More specifically, the Examiner is of the view that the genus a "second" prostate-specific mRNA" (now recited as "a prostate-specific mRNA") was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner contends that the written description in this case only sets forth PSA as a second prostate-specific marker.

Applicant respectfully disagrees. The Examiner is referred, for example, to paragraph **[0069]** on page 7, which defines what is intended by a prostate-specific marker:

> As used herein the terminology "prostate specific marker" relates to any molecule whose presence in the sample indicates that such sample contains prostate cells (or a marker therefrom). Therefore a "prostate specific sequence'' refers to a nucleic acid or protein sequence specifically found in prostate cells and usually not in other tissues which could "contaminate" a particular sample. For certainty, when a urine sample is used, the second prostate specific marker according to the present invention does not have to be solely expressed in the prostate. In fact markers which are solely expressed in one organ or tissue is very rare. . . . Thus, when urine is the sample, this second prostate-specific marker is not normally expressed in other types of cells (e.g., cells from the urinary tract system) to be found in the urine sample.

The specification further states "[t]he sample is also tested for the presence of second prostate-specific marker (e.g., PSA, hK2/KLK2, PSMA, transglutaminase 4, acid phosphatase, PCGEM1 mRNA or fragments thereof) to control for the presence of prostate cells in the sample (or their number) as well as to further control a negative or positive result obtained with the detection of PCA3. The second prostate specific marker may also be a prostate specific PCA3 RNA that is not associated with prostate cancer but is expressed in prostate cells." Specification at paragraph **[0084]**. Further, paragraph **[0102]** of the specification recites sequences of such prostate specific markers and provides references that describe such markers. Moreover, the specification at paragraph **[0105]** recites a PCA3 sequence associated with a non-malignant state of the prostate that could be used as the prostate-specific marker. Lastly, paragraphs **[0106]**, which provides GenBank accession numbers of sequences of such prostate-specific markers. Paragraphs **[0116]** and **[0126]** of the specification provide further support for the claims in the specification.

The Applicant therefore respectfully submits that the disclosure provides **(1)** a sufficient number of species and the means to select and use them to constitute a substantial portion of the claimed genus; and **(2)** sufficient descriptive, structural and functional features which are common to the genus (e.g., paragraph **[0069]**). Clearly, the person skilled in the art to which the present invention pertains would, in view of the teachings in the application and common general knowledge, know which markers could be selected and used as a prostate-specific marker.

The Examiner also objects to the genus of molecular beacons (see claim 52). The Examiner asserts that the written description in this case only sets forth SEQ ID NO:6 and SEQ ID NO:5 as examples of molecular beacons (see claim 53).

Applicant respectfully disagrees. The Examiner is referred to paragraphs **[0115]** to **[0117]**, which clearly support the genus for molecular beacons. In any event, in order to clarify that not "any" beacon is comprised in the claimed genus, the recitation of

"molecular beacons" was amended to specify that same is specific towards its target (i.e., PCA3 or PSA).

The Applicant therefore respectfully submits that the disclosure provides **(1)** sufficient descriptive, structural and functional features which are common to the molecular beacon genus (e.g., paragraphs **115** to **117**); and **(2)** attributes or characteristics in the claims (i.e., PCA3-specific or PSA-specific) to support the claimed genus. Clearly, the person skilled in the art to which the present invention pertains would, in view of the teachings in the application and general knowledge, know which beacons could be selected and used in accordance with specific embodiments of the present invention. Indeed, in *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) the Federal Circuit reaffirmed the principle that a "patent need not teach, and preferably omits, what is well known in the art." *Id.*, quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987). As noted above, the state of the art as of the effective filing date of the above-identified was advanced and one of skill in the art would be aware of suitable prostate markers and molecular beacons.

In view of the above and foregoing it is respectfully submitted that the Applicant was in possession of the claimed genus at the time of the invention as supported by the disclosure, and thus requests that the Examiner withdraws the rejection of claims 41- 69 under 35 U.S.C. § 112, first paragraph for lack of written description.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT REJECTION)

Claims 41-69 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification is deemed not to enable any person skilled in the art to which it

pertains or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

More specifically, the Examiner is of the view that "while being enabling for a method for determining a predisposition for or the presence of prostate cancer in a patient...using a second primer pair specific to PSA mRNA...**the specification does not reasonably provide enablement for a method** for determining a predisposition for or the presence of prostate cancer in a patient...**[a]** using a second primer specific to a "second prostate-specific mRNA"...**[b]**correlating, in just any way...**[c]** any type of risk" (page 10 of Official Action). The Examiner also alleges lack of enablement for **[d]** "just any molecular beacon" (page 11 of the Official Action).

Applicant traverses the rejection as follows. Firstly, it is submitted that the amendments to **claims 41 and 67**, to specify how a level of PCA3 is indicative or not of a high or low risk of prostate cancer and the removal of the terminology "correlating", have rendered the rejections moot with respect to **[b]** and **[c],** above. Similarly, Applicant respectfully submits that the amendments to **claims 52 and 55** to specify that the molecular beacon "hybridizes to PCA3 [or PSA] under high stringency conditions" has rendered the rejection moot with respect to **[d],** above. For the record, Applicant believes that the skilled artisan would not comprehend "molecular beacon" as any molecular beacon, since a targeting of specific sequences is responsible and required for the workings of the beacon technology.

With respect to the prostate-specific marker (previously recited as "second prostate-specific marker"), the Examiner is respectfully referred to the arguments given above concerning the lack of written description concerning same (starting at page 12). Applicant agrees with the Examiner that the disclosure provides clear enablement with PSA. Applicant further submits that the disclosure, in providing a definition as to how one chooses such a prostate-specific marker, enables the skilled artisan cognizant of the common general

knowledge, to select and use other prostate-specific markers without undue experimentation. The Examiner will note other listed examples of prostate-specific markers which can be used in accordance with the present invention (*hK2/KLK2* and *PSMA* (of the kallikrein family, similarly to PSA), *transglutaminase 4, acid phosphatase, PCGEM1 mRNA or fragments thereof, and the PCA3 sequence associated with a non-malignant state of prostate cancer*).

The Examiner also discusses the "high" unpredictability in disease detection. Applicant respectfully submits that the diagnosis method of the present invention is in fact of "high" predictive value. Indeed, the positive predictive value (PPV) of the test of the present invention is 75% and the negative predictive value (NPV) thereof is 84% (paragraph **177**). The current gold standard in prostate cancer diagnosis is based on PSA detection and as described herein its PPV and NPV are 38% and 80%, respectively (also in paragraph **177**). The Examiner is referred to the disclosure as a whole, and more particularly to paragraphs **174-177** ("the overall accuracy of the method is 81% as compared with an accuracy of 47% for tPSA", at the end of paragraph **177**), for further support for the predictability of prostate cancer detection based on the methods as claimed. The present invention shows for the first time not only that PCA3 mRNA can be detected in urine and that together with the detection of a prostate-specific mRNA, an accurate determination of the prostatic state of the patient can be determined, but also that the claimed method is more accurate than the current gold standard method based on PSA detection.

The Examiner alleges at page 15 of the Official Action that "the specification has not demonstrated that just any prostate-specific mRNA can be used in place of PSA". Applicant respectfully submits that while the disclosure does not provide data *per se* with other markers, it provides clear enablement as to: **(1)** how to select a prostate-specific marker, **(2)** what characteristics this marker should have, **(3)** a list of such markers, and **(4)** sequences of such examplified markers. Taken together, it is reiterated that the skilled artisan would not need any undue experimentation to choose a prostate-specific mRNA that could be

detected in accordance with the claimed methods in order to validate the lack of mRNA detection of PCA3 from a urine sample.

Applicant respectfully submits that as now presented, the claims do not cover "any" level of PCA3 to be correlated "in every way with every type of risk". Also, the claims do not cover "just any molecular beacon" as explained in the above section relating to written description.

In view of the above and foregoing, Applicant respectfully requests that the Examiner withdraws his rejection of the claims under 35 U.S.C. § 112, first paragraph for lack of enablement.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 41-50, 57, 58, 61-63, and 65-68 are rejected as being allegedly unpatentable over Bussemakers *et al.*, (US 7,008,765 B1) in view of Clements *et al.*, 1999 (J. Urol. 161: 1337-1343) under 35 U.S.C. § 103(a). Applicant traverses this rejection as follows.

Applicant agrees with the Examiner that Bussemakers teaches "performing an RT-PCR RNA amplification assay on prostate biopsy sample" [our emphasis]. However, the Applicant respectfully disagrees with the Examiner's contention that Bussemakers teaches "wherein an absence of PCA3 mRNA or a lower level of PCA3 mRNA as compared to the level of PCA3 mRNA in a sample from a normal subject, indicates that said patient will not develop prostate cancer and that said patient does not have prostate cancer, when PSA mRNA is detected (Example 2, in particular)" [our emphasis]. Applicant respectfully submits that Example 2 does not even hint at the use of PSA (or another prostate-specific marker) to validate the diagnostic method based on PCA3 detection. What Bussemakers teaches is that PCA3 products detection allows a clear distinction between benign and

malignant specimens while "PSA and PSM could not make this distinction: approximately equal amounts of product were found in normal and tumor samples". Applicant also disagrees with the Examiner's contention that Bussemakers teaches a method in which the "amplification of PCA3 and said PSA mRNA is performed simultaneously (column 36, in particular)". In fact, the term "simultaneously" is found only once in Bussemakers in the context of digesting the vector pMB9 with two restriction enzymes "simultaneously".

The Examiner also states "by teaching PSA mRNA is detected in both benign and malignant prostate samples and that the level of PSA mRNA is not a reliable indicator of prostate cancer disease state, Bussemakers teaches a method wherein detection of PSA would validate a negative result for PCA3 detection in that the detection of PSA mRNA is indicative of the presence of prostate cells in a sample that did not display elevated PCA3 levels (Example 2, in particular)". Applicant respectfully disagrees. As discussed above, Bussemakers is silent on a detection of an additional prostate-specific marker from the same sample to validate the results using PCA3. Nowhere in Bussemakers is there a suggestion that RNA amplification could be performed using PCA3 and a prostate-specific marker (such as PSA) and to correlate the absence of PCA3 with an absence of a lower risk of developing prostate cancer when the prostate-specific marker is detected. In addition, Bussemakers indicates in column 37 (at lines 6-8), and in column 38 (at lines 28-37), that PSA expression was decreased in malignant versus benign tissues. Thus, PSA expression is a negative indicator of malignancy status. Accordingly, PSA may not be equivalently useful for detecting and quantifying normal cells and cancer cells because expression of the gene product is not constant. Thus, despite Applicant's choice of preferred prostate-specific sequences to be detected in addition to PCA3, Bussemakers may provide reasons **not** to use nucleic acid markers such as PSA, human kallikrein 2, PSMA..., as markers to validate the diagnostic methods of the invention (last paragraphs of claims 41 and 67).

The Examiner also alleges that Bussemakers teaches a method where the "amplification of PCA3 and said second prostate specific nucleic acid is performed

simultaneously in one container (see column 36, in particular)". Applicant respectfully disagrees as this teaching is not found in column 36 or elsewhere in Bussemakers.

Applicant agrees with the Examiner that Bussemakers does not specifically teach methods using a urine sample, a voided urine sample from a patient having an increased number of prostate cells therein, urine sample containing semen or a urine sample collected following a digital rectal exam. The Examiner, however, alleges that "these deficiencies are made up in the teachings of Clements *et al.* " Clements indeed teaches a method using RT-PCR to detect PSA mRNA in patient samples. However, and of importance, all the samples of Clements are post-ejaculation samples except for two samples shown in Figure 2 and identified as "Other Urines" in the figure legend thereof and identified as "pre". One of these two samples is also labelled as "Vas" because it came from a vasectomized patient (see the "Other Urines " panel at the right-hand side of Figure 2). Of note, only one of the two regular urine samples enables a detection of PSA (the "Vas" sample; the non-"Vas" "pre" sample does not detect it; see the middle pannel "PSA RT-PCR"). Thus, the use of urine which does not contain semen is clearly not validated by Clements. In fact, Clements itself corroborates this contention at page 1342, bottom left column when it is stated "since the result were comparable between ejaculate and urethral washings (defined as "the first urinary void immediately after masturbation") from both groups of patients and control subjects, it is possible that urethral washings specimens could be used instead of ejaculate for this assessment in the future. Thus, even for the urethral washings, which are post-ejaculation samples and thus contain sperm/semen, there is a doubt in Clements as to their value for diagnosis. Clements then goes on to cite Iwakiri *et al.*, (1993; provided herewith for the Examiner's convenience), and based thereon, Clements states "suggests urines, per se, may be very useful" (our emphasis added). Thus again, there is doubt in Clements as to the usefulness of a urine sample. Of note, Iwakiri is concerned with PSA protein detection, not PSA RNA in urine samples. Furthermore, Iwakiri states (at the end of the Abstract) "This finding diminishes the chance that the first voided urine PSA level will be a useful marker to detect locally recurrent tumor after radical prostatectomy".

Thus, Iwakiri and/or Clements do not teach that a regular urine sample (e.g., a voided urine sample pre-ejaculation) is a suitable sample for the detection of the unstable RNA molecule. Actually, Clements and Iwakiri can be viewed as teaching away from the use of regular urine samples for prostate cancer assessment, as claimed, because the skilled artisan would neither be tempted nor motivated to use such urine samples, based on **(1)** the lack of predictability of the results of Clements with its two urine samples; **(2)** the uncertainty of Clements that the urethral washings could replace the semen sample (ejaculate), and thus the further uncertainty to attempt using a "urine sample having not been obtained immediately following ejaculation" because it would contain even less semen than the doubtful urethral washings; and **(3)** the combined teaching of Iwakiri and Clements as to the uncertainty of the use of urine for prostate cancer assessment when knowing that RNA is a macromolecule which could be degraded in urine.

The Examiner claims that Clements which is only concerned with semen-containing samples further "teaches methods using urine samples from patients that have had digital rectal exams (left column of page 1338, in particular)". The Applicant respectfully disagrees with this contention because the samples of Clements were not obtained following digital rectal exams (DRE). The DRE only served to recruit the patients in the study (page 1338, left column). "*Subjects.* Seventy-seven patients who underwent TRUS-guided prostatic biopsies on the basis of an abnormal serum PSA (>4ng./ml.) and/or an abnormal digital rectal examination, were recruited into the study" [our emphasis].

The Examiner also alleges that Clements "teaches that the PSA mRNA expression is intended to be used as a marker for prostate cells when screening patients for mRNA markers that are up regulated in prostate cancer cells of patients with prostate cancer (see paragraph flanking 1340-1341, in particular)." The Applicant once again respectfully disagrees with this interpretation. The quote referred to by the Examiner is the following: "since we were unable to discriminate between controls and patients using PSA and PSM, another marker, Apolipoprotein-D, which has been shown by immunostaining to be elevated

in prostatic cancers compared with immediately adjacent non-malignant tissue, was used" [our emphasis]. Thus, Apo-D is only used to further assess whether urethral washings following ejaculation, can replace semen samples for molecular diagnostic. Of further note, Clements concludes in the abstract, "we have established a sensitive method of detecting prostatic cells in ejaculate and urethral washings and shown that PSA RT-PCR is a reliable indicator of prostate cells in these samples. However, RT-PCR for PSA, PSM and Apolipoprotein-D were not useful for discriminating malignant from non-malignant prostate cells". Clements does not teach that RT-PCR from urine samples *per se* can be used to detect prostate cells therein and it fails to teach a usefulness in using mRNA detection for assessing the malignant state of the prostate.

Applicant reiterates that as amended, the independent claims of the present invention clearly recite that the urine samples are not obtained like those of Clements following ejaculation. In view of the above and foregoing, it should be clear that Clements (alone or together with other cited art) does not suggest the use of urine *per se* as a sample for mRNA detection and prostate cancer diagnosis.

Applicant respectfully submits that prior to the present invention, the use of a quantitative assay to measure PCA3 RNA and a prostate-specific RNA in urine had not been suggested, and surely had not been carried out. Applicant further submits that prior to the present invention, there was no "reasonable likelihood" of success that a urine-based test could be used to diagnose prostate cancer based on the detection of PCA3 RNA (a macromolecule considered in the art as unstable) and a prostate-specific RNA.

Applicant invites the Examiner to consider Fradet et al., 2004 (Urology 64(2): 311-316 [including an "Editorial Comment" from p315-316; enclosed herewith]; the scientific article corresponding to the instant invention). In the "Editorial Comment" the pionneering nature of the present invention is corroborated:

> In this report Fradet et al., present the results of a multicenter study on the diagnostic value of the first gene-based test for prostate cancer...
>
> The first exploratory study by Hessels et al. [July 2003] indicated that gene-based testing for the diagnosis of prostate cancer was feasible and that the use of a relatively novel substrate (i.e., urinary sediment after extended DRE), was very promising. Fradet et al., now provide additional evidence that uPM3 test **can predict the presence of prostate cancer with extremely high accuracy. This will have profound additional value** within the PSA range of 4 to 10 ng/ml, because very of high NPV resulting from the high specificity of the test (89%). I therefore conclude that we are on the verge of the clinical introduction of a gene-based test for prostate cancer. [Our emphasis]

Finally, Applicant respectfully submits that, as per §2143.03 of the MPEP, in order "to establish *prima facie* obviousness of a claimed invention, **all** the claim limitations must be taught or suggested by the prior art". Since Bussemakers and Clements (or together with any of the references cited below) do not teach or suggest a method combining the detection of **both** PCA3 mRNA and a prostate-specific mRNA in **a urine sample** having not been obtained immediately following ejaculation, to determine the presence / absence / predisposition to develop prostate cancer and comprising a determination of an absence of or a lower risk of developing prostate cancer when **in the absence of detection of PCA3, the prostate-specific marker is detected**, it does not teach or suggest **every element** of independent claims 41 and 67.

In view of the above and foregoing, which supports the pioneering nature of the urine-based diagnostic methods claimed, the Examiner is requested to withdraw the obviousness rejection based on the combination of Bussemakers with Clements.

Claims 41-50, 57, 58, 61-63, and 65-68 are also rejected as being allegedly unpatentable over Bussemakers *et al.*, in view of Clements *et al.*, and in further view of Cheung *et al.*, 1994 (J. Clin. Microbiol., 32:2593-2597) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Cheung, concerning the use of silica particles for nucleic acid purification, do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample having not been obtained immediately following ejaculation, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Cheung does not render the claimed methods of the invention obvious.

Claims 41-50, 57, 58, 59-63, and 65-69 are also rejected as being allegedly unpatentable over Bussemakers *et al.*, in view of Clements *et al.*, and in further view of Baret (EP 0 256 932 A2).

Applicant respectfully submits that the teachings of Baret concerning chemiluminescent assays do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample having not been obtained immediately following ejaculation, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Baret does not render the claimed methods of the invention obvious.

Claims 41-51, 54, 57, 61-63, and 65-68 are also rejected as being allegedly unpatentable over Bussemakers *et al.*, in view of Clements *et al.*, in further view of Buck *et al.*, 1999 (Biotechniques 27(3): 528-536) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Buck concerning the design of probes and primers do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a

prostate-specific RNA in a urine sample having not been obtained immediately following ejaculation, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Buck does not render the claimed methods of the invention obvious.

Claims 41-50, 52, 53, 55, 56, 57, 58, 61-63, and 65-68 are further rejected as being allegedly unpatentable over Bussemakers *et al.*, in view of Clements *et al.*, in further view of Schlegel *et al.*, (US 2002/0168638 A1) under 35 U.S.C. § 103(a).

Applicant respectfully submits that the teachings of Schlegel concerning a large number of markers alleged to be usable in "detecting, characterizing, preventing and treating prostate cancers", and in particular prostate protein markers, do not correct the defects of the combination of Bussemakers and Clements in teaching a method combining the detection of both PCA3 RNA and a prostate-specific RNA in a urine sample having not been obtained immediately following ejaculation, to determine the presence / absence / predisposition to develop prostate cancer. In view of the above and foregoing, the combination of Bussemakers with Clements and Schlegel does not render the claimed methods of the invention obvious.

NEW MATTER

Claim 66 is rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Claim 66 has been cancelled, thereby rendering this rejection moot. Applicants reserve the right to prosecute the subject matter thereof (which is supported in the disclosure for example in paragraph **025,** as mentioned above) in further applications.

Claim 41 and dependent claims 42-66 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. This rejection

has been rendered moot by the amendment of claim 41 which no longer recites "correlating... to a PCA3 mRNA".

CONCLUSION

Prompt and favorable consideration of this Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Cynthia M. Bouchez
Attorney for Applicants
Registration No. 47,438

Date: Sept. 20, 2007
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600